

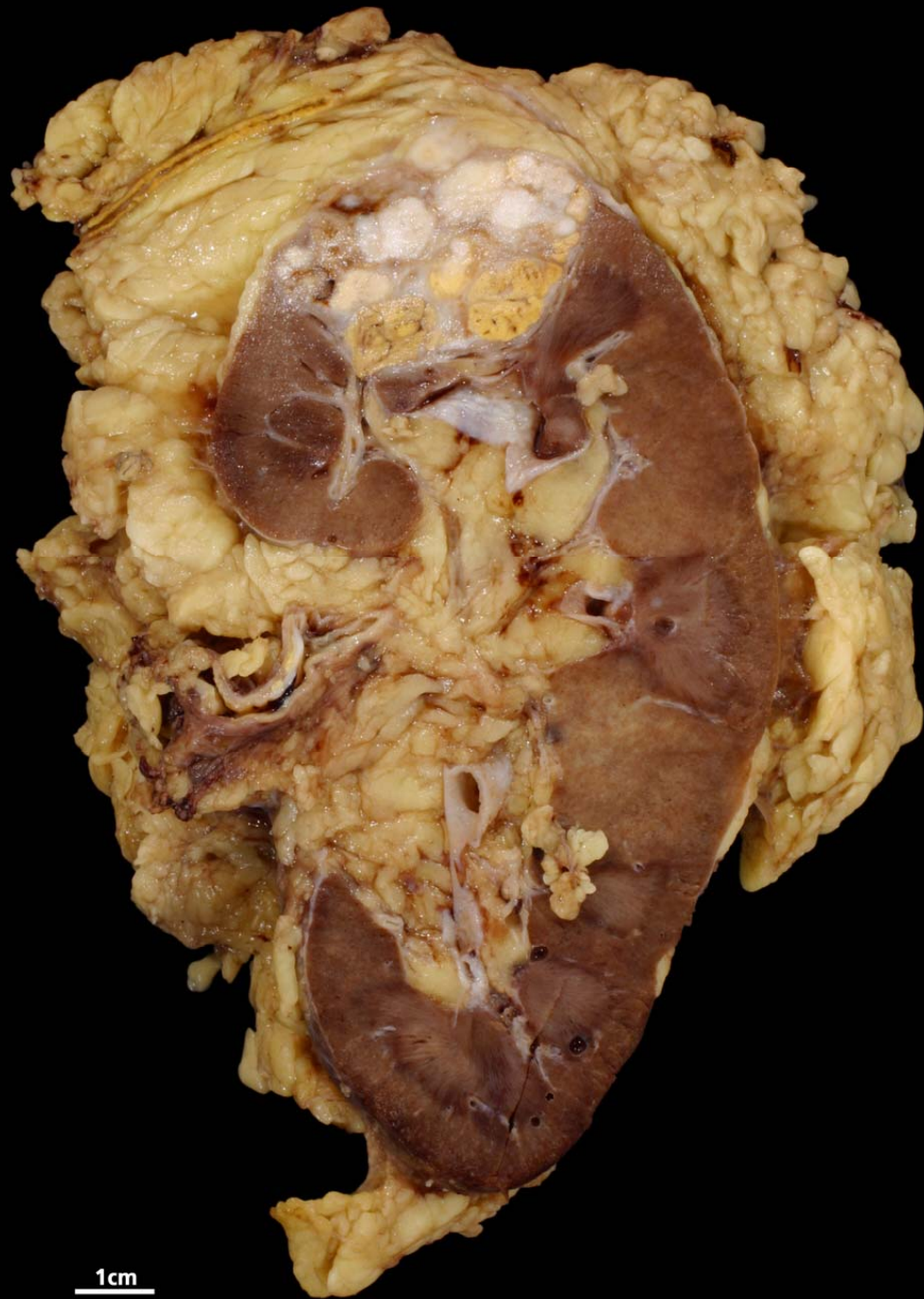
# Survival Analysis by Computational Pathology

Thomas Fuchs

**ETH**

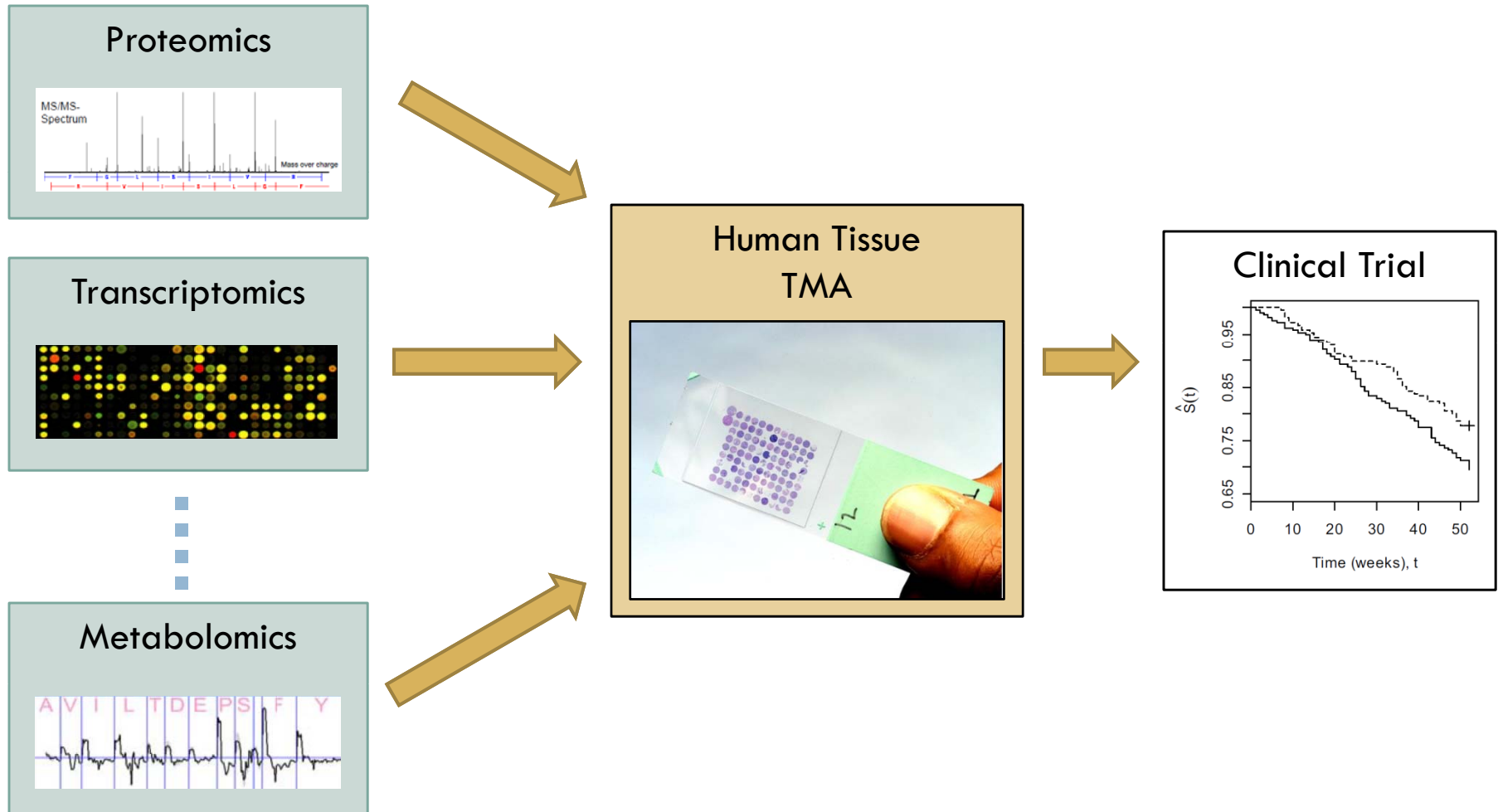
Eidgenössische Technische Hochschule Zürich  
Swiss Federal Institute of Technology Zurich



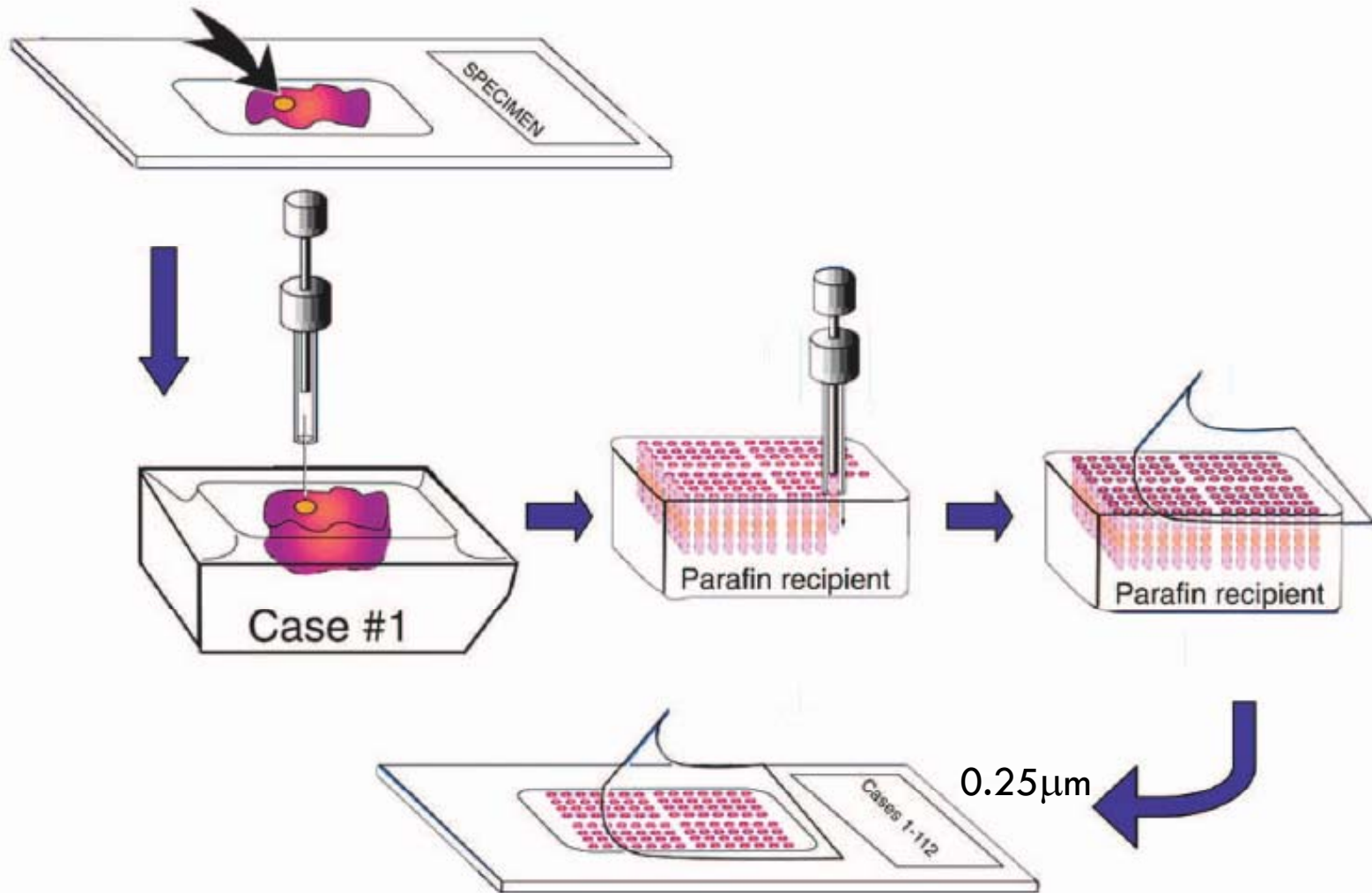


1cm

# Biomarker Detection & Validation

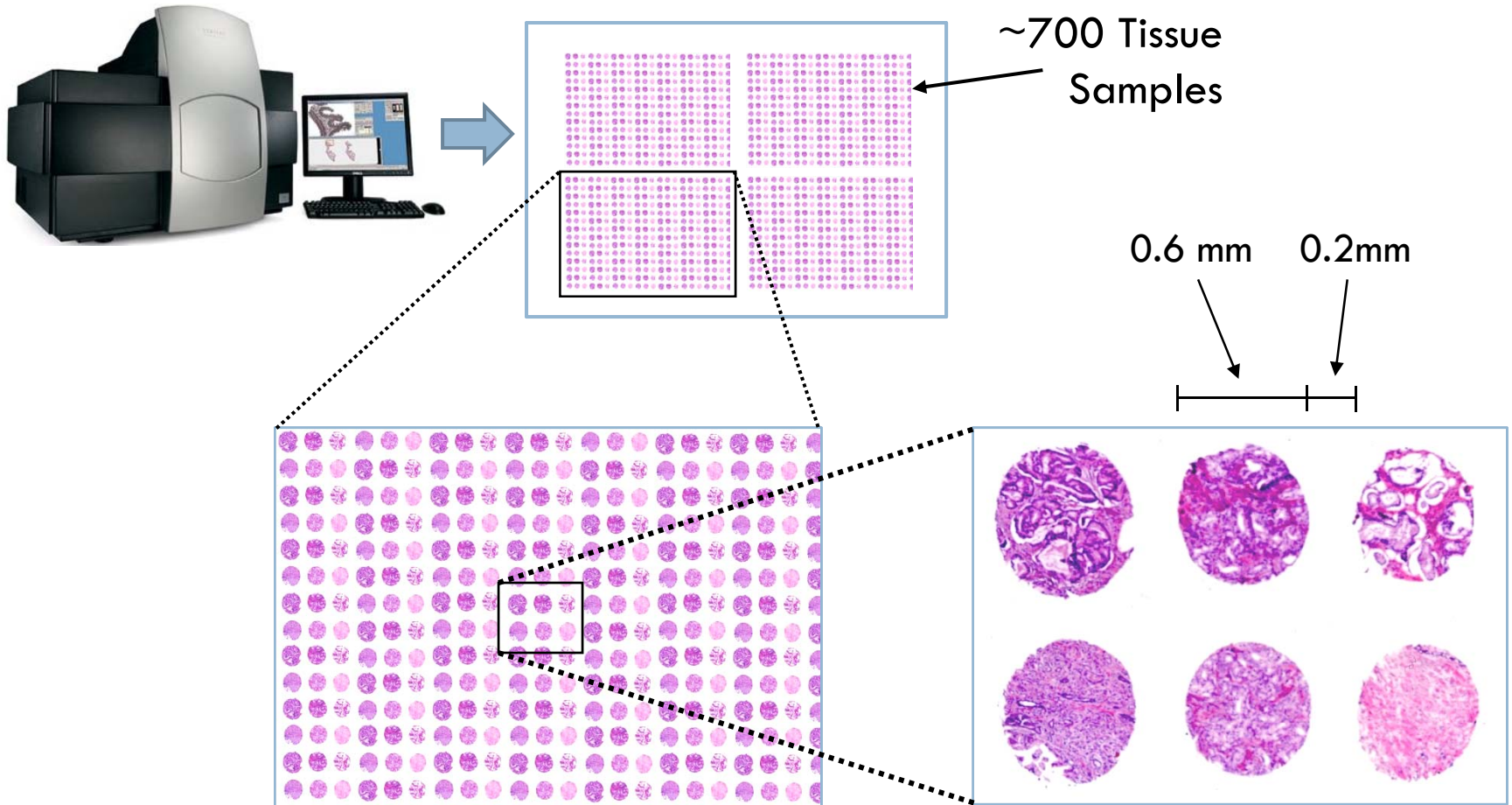


# TMA Preparation

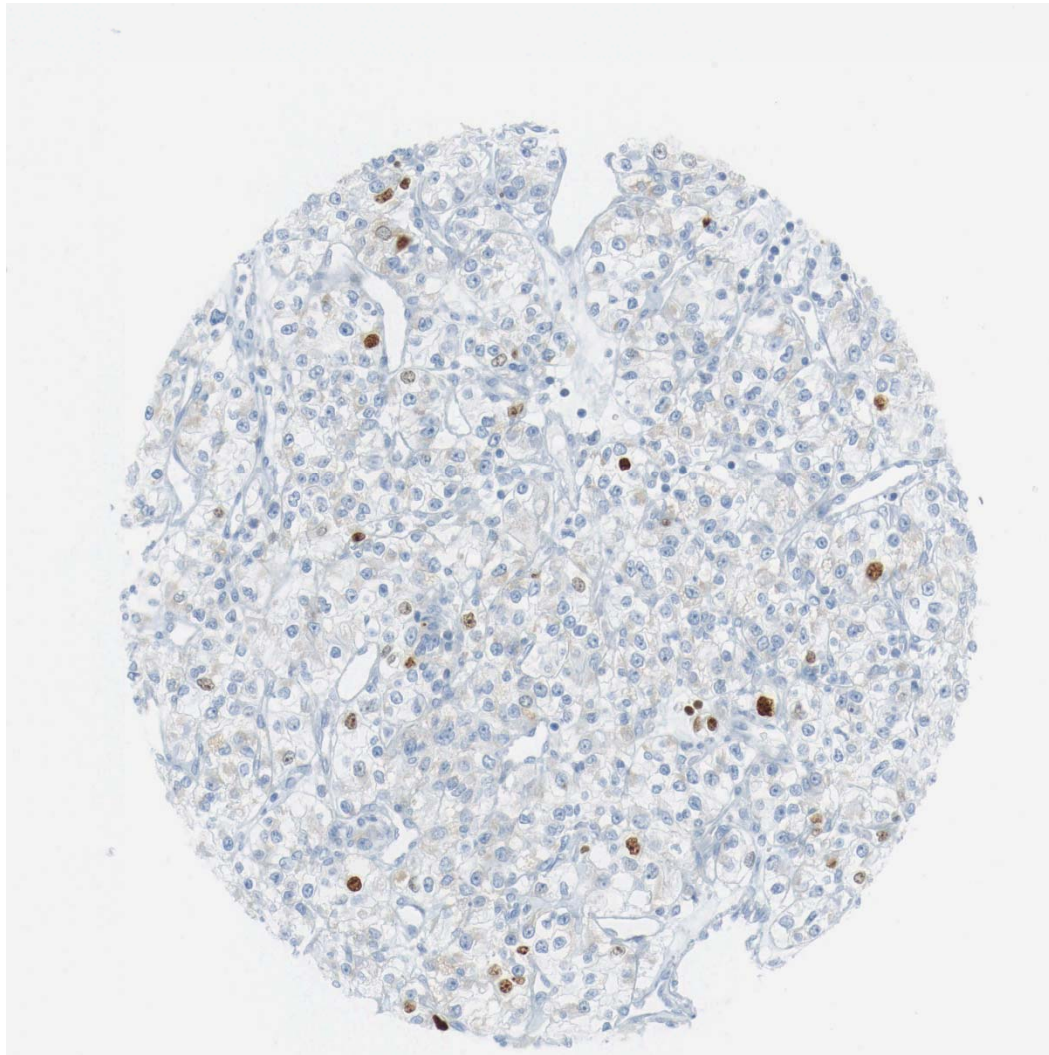




# Tissue Array Section



# TMA Spot with MIB-1 (KI-67) Antigen



1 image for each patient

40x magnification

resolution of  $0.25\mu\text{m}$

3000 x 3000 Pixels

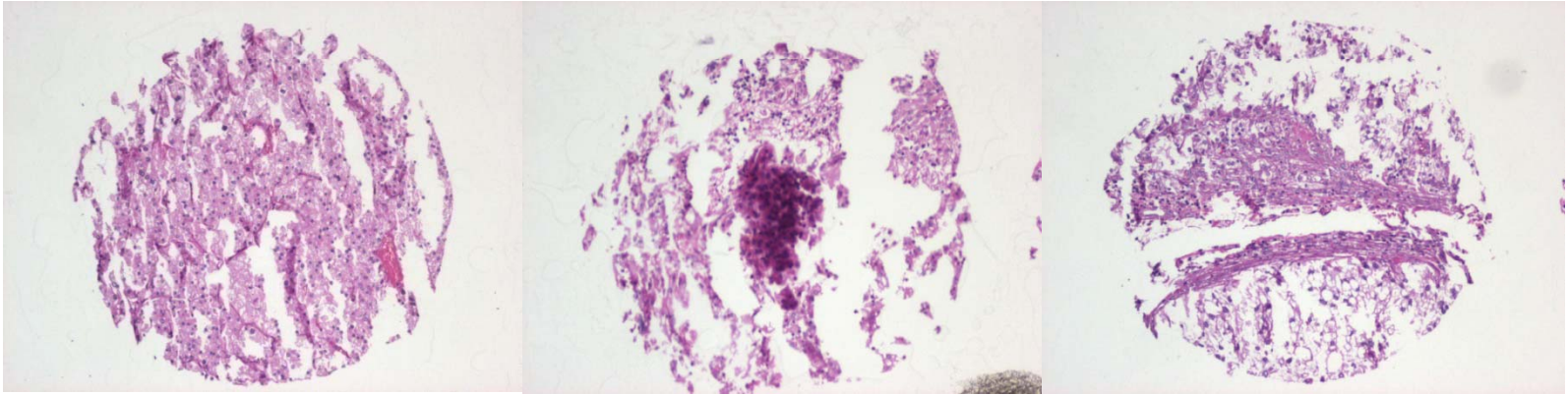
# From a qualitative to a quantitative science

- At the beginning of the 21st century pathology is still a **qualitative science**.
- It relies purely on **subjective estimations** by human experts.
- The goal is to lead pathology from a qualitative to a **quantitative science**.
- Machine learning and computer vision are **enabling technique** to achieve this ambitious goal.

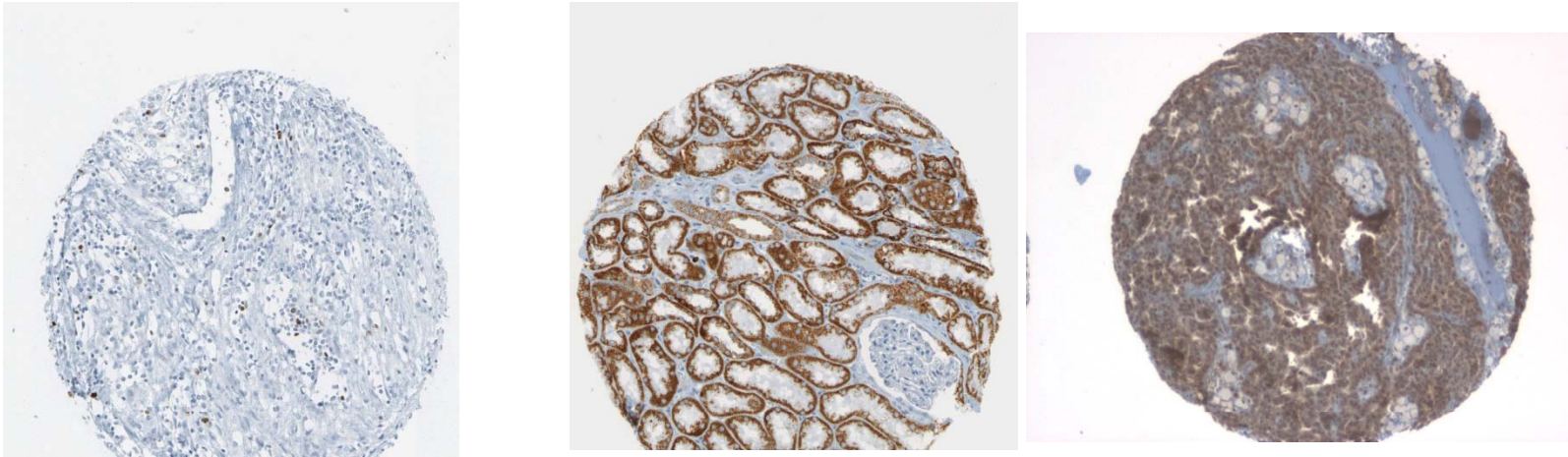


# Variability

H & E



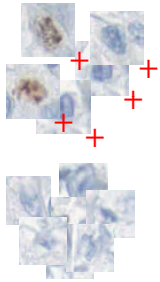
MIB-1



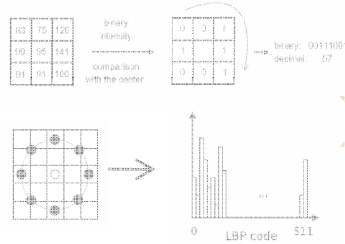


# Comp. Path. Framework

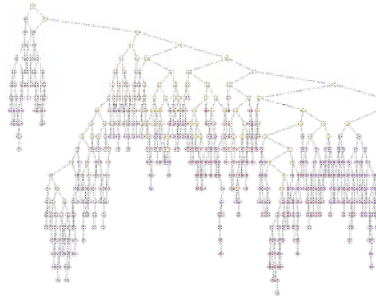
## 1 Training Samples



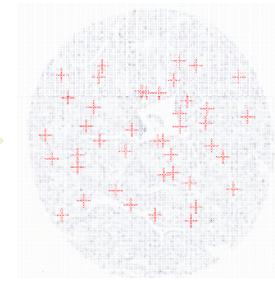
## 2 Feature Extraction



## 3 Random Forest Learning



## 4 Nuclei Detection

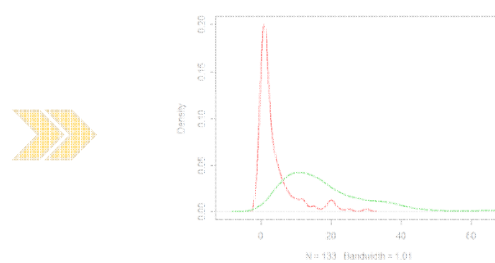


## 5 Staining Estimation

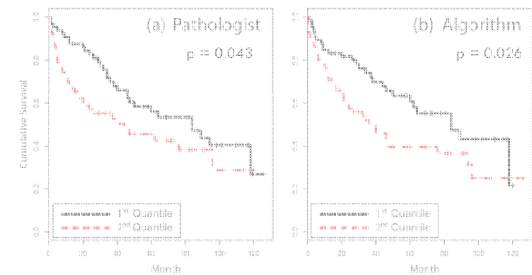
5%



## 6 Application to Patient Cohort



## 7 Estimated Marker Distribution



## 8 Survival Analysis

**What is the „Ground Truth“?**

**Is there any „Ground Truth“?**

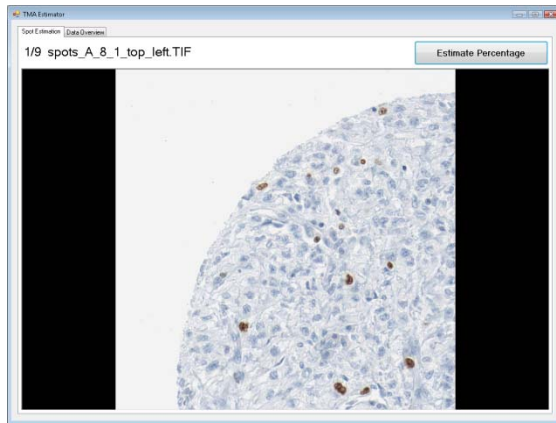
**There is**

**NONE**



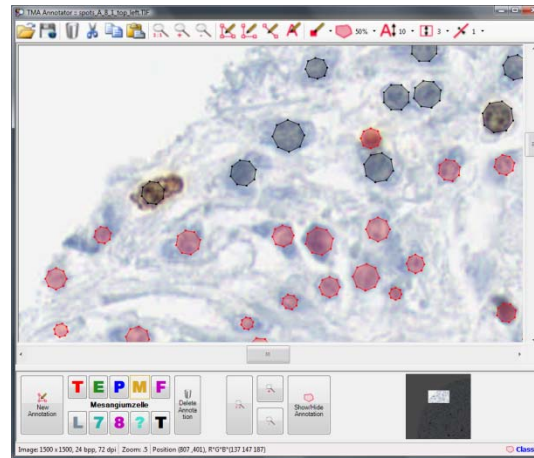
# Generating a Gold Standard

## TMA Estimator



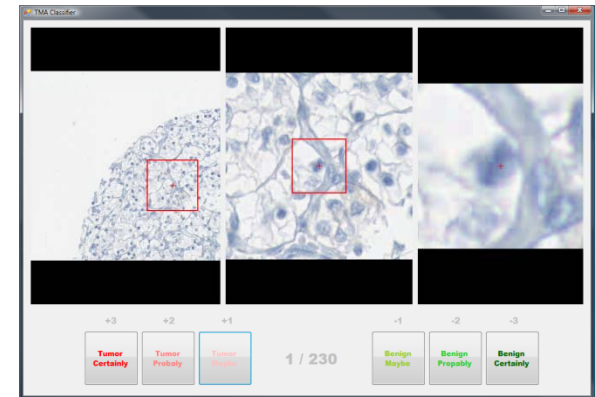
Estimate the Staining on a whole Spot

## TMA Annotator



Detect nuclei on a whole Spot

## TMA Classifier

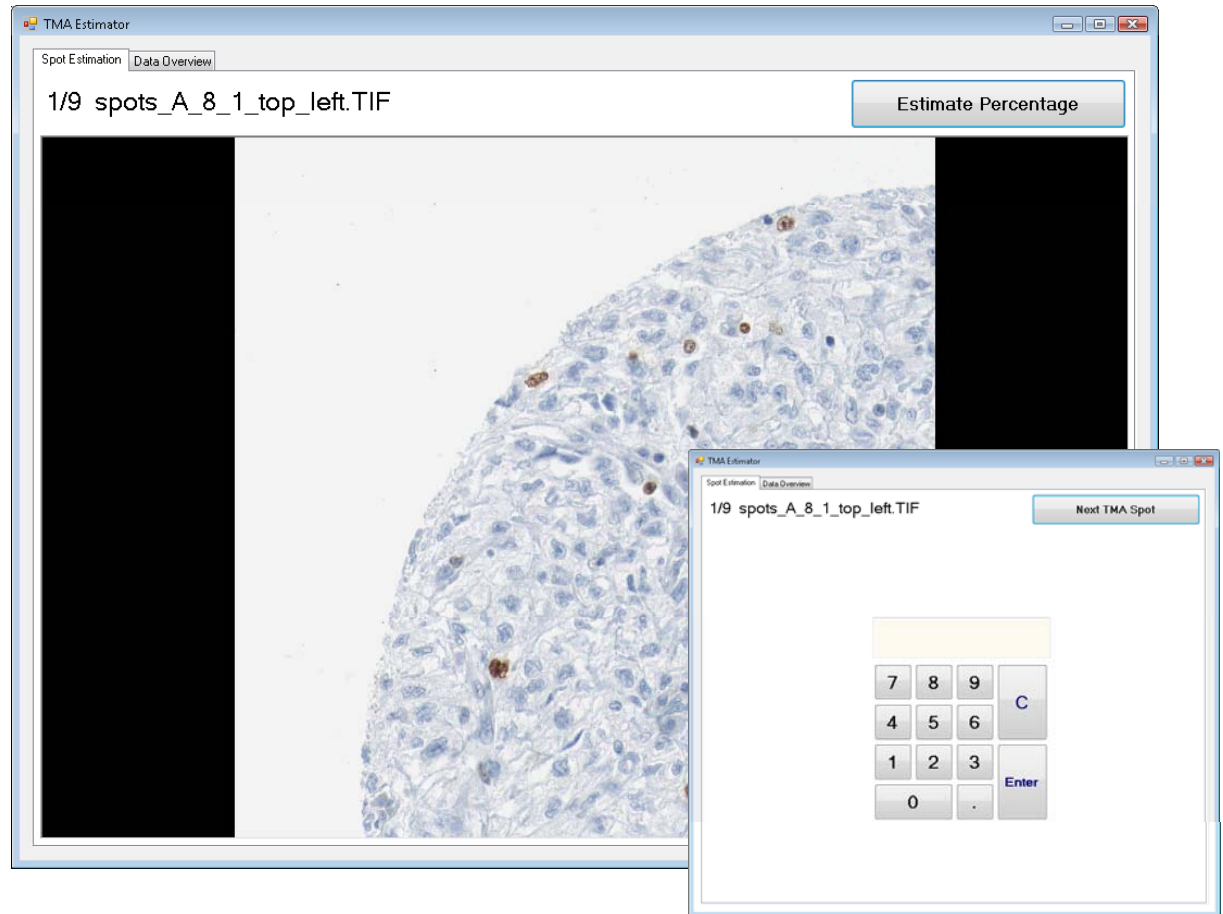


Classify single nuclei into tumor, non-tumor and stained, not-stained

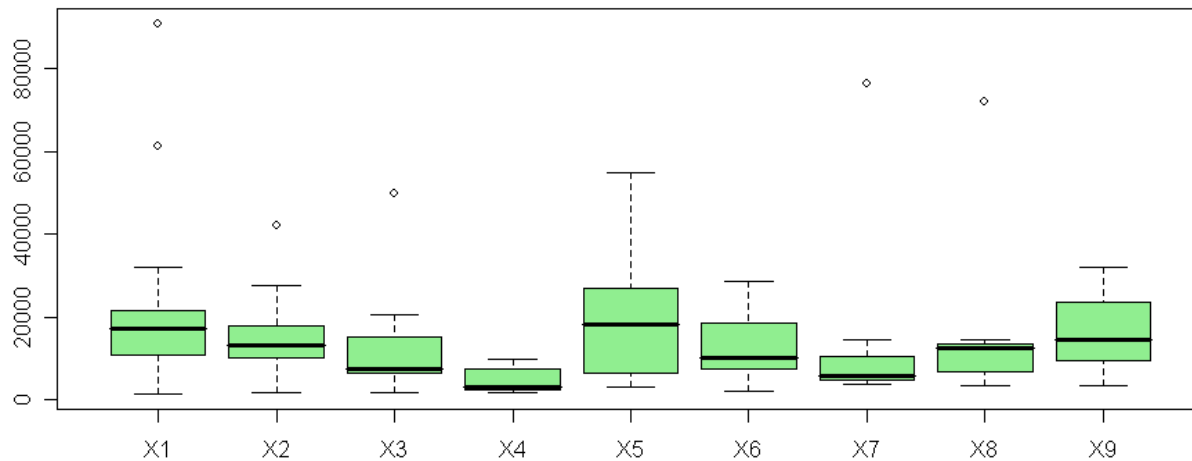
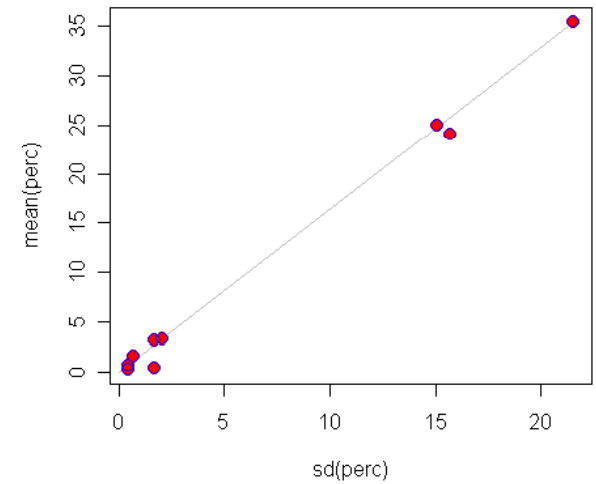
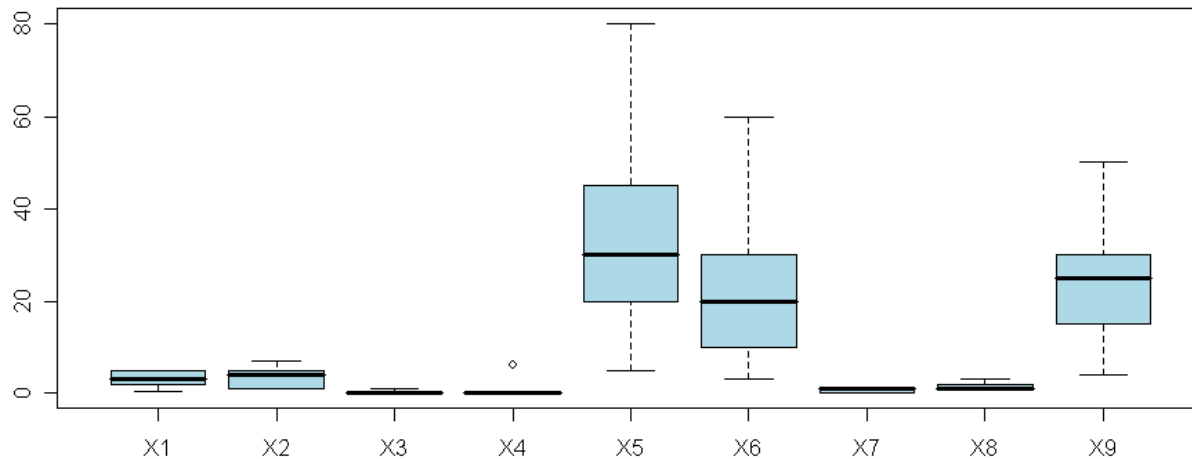
# TMA Estimator



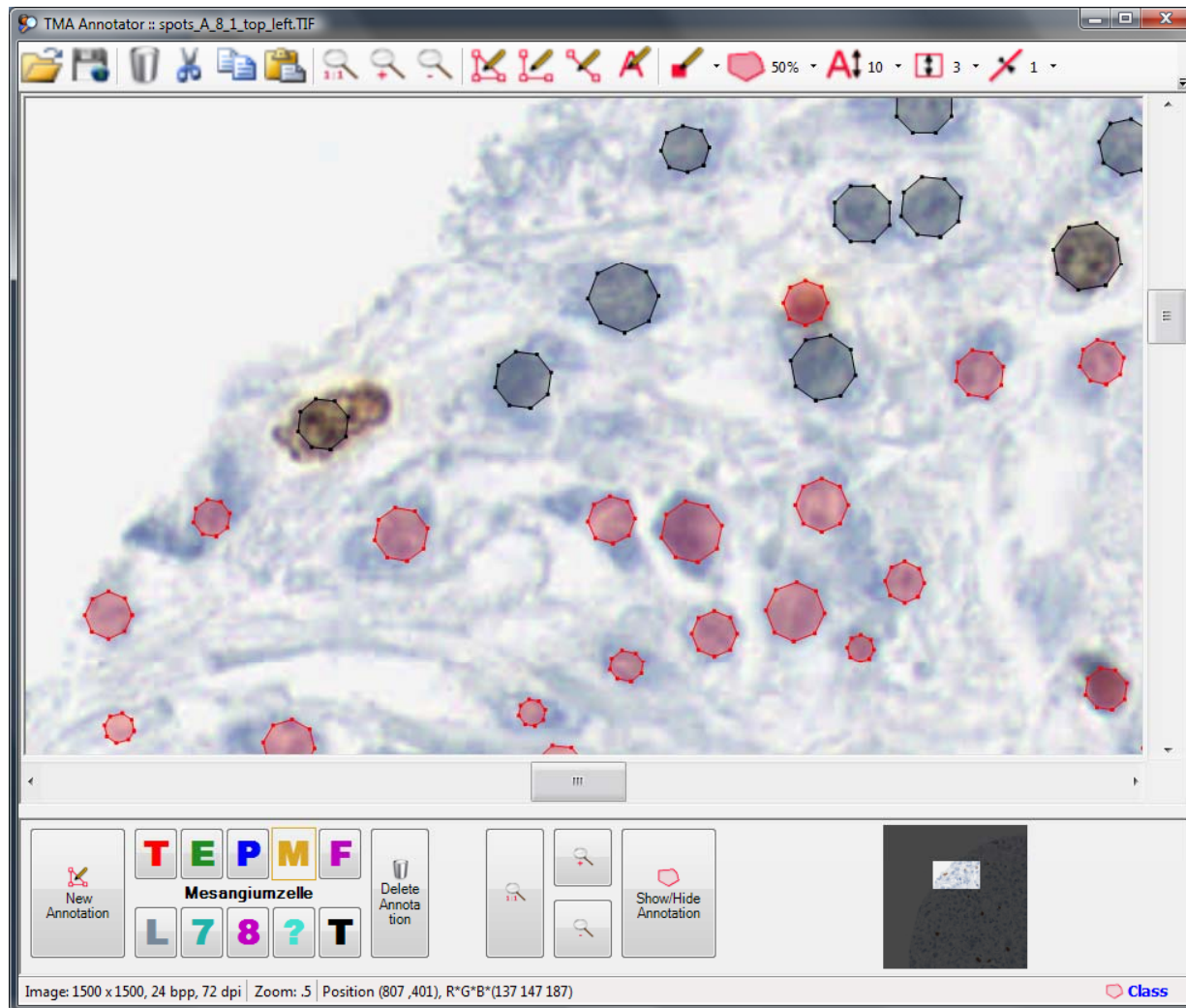
Labeling Tool  
for Pathologists  
on Tablet PC



# Estimated Staining



# TMA Annotator

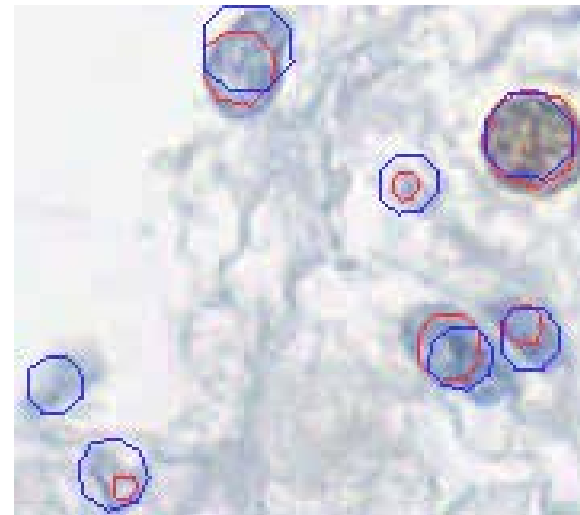




# TMA Annotator



- 2 pathologists
- >2000 nuclei
- 15% detection mismatch



# TMA Classifier - Tumor

The screenshot displays the TMA Classifier software interface. It features three histological images of tissue sections, each with a red square highlighting a specific region of interest. The first image on the left shows a low-magnification view of a tissue section with a red square and a red crosshair. The second image in the middle shows a higher magnification of the same tissue, with a red square and a red crosshair. The third image on the right shows a very high magnification of a single cell, with a red square and a red crosshair. Below the images, there are six classification buttons arranged in two groups. The first group, labeled '+3', '+2', and '+1', contains buttons for 'Tumor Certainly', 'Tumor Probaly', and 'Tumor Maybe'. The second group, labeled '-1', '-2', and '-3', contains buttons for 'Benign Maybe', 'Benign Propably', and 'Benign Certainly'. The button 'Tumor Maybe' is currently selected, indicated by a blue border. In the center of the interface, the text '1 / 230' is displayed.

TMA Classifier

+3 +2 +1 -1 -2 -3

**Tumor**  
Certainly

**Tumor**  
Probaly

**Tumor**  
Maybe

1 / 230

**Benign**  
Maybe

**Benign**  
Propably

**Benign**  
Certainly

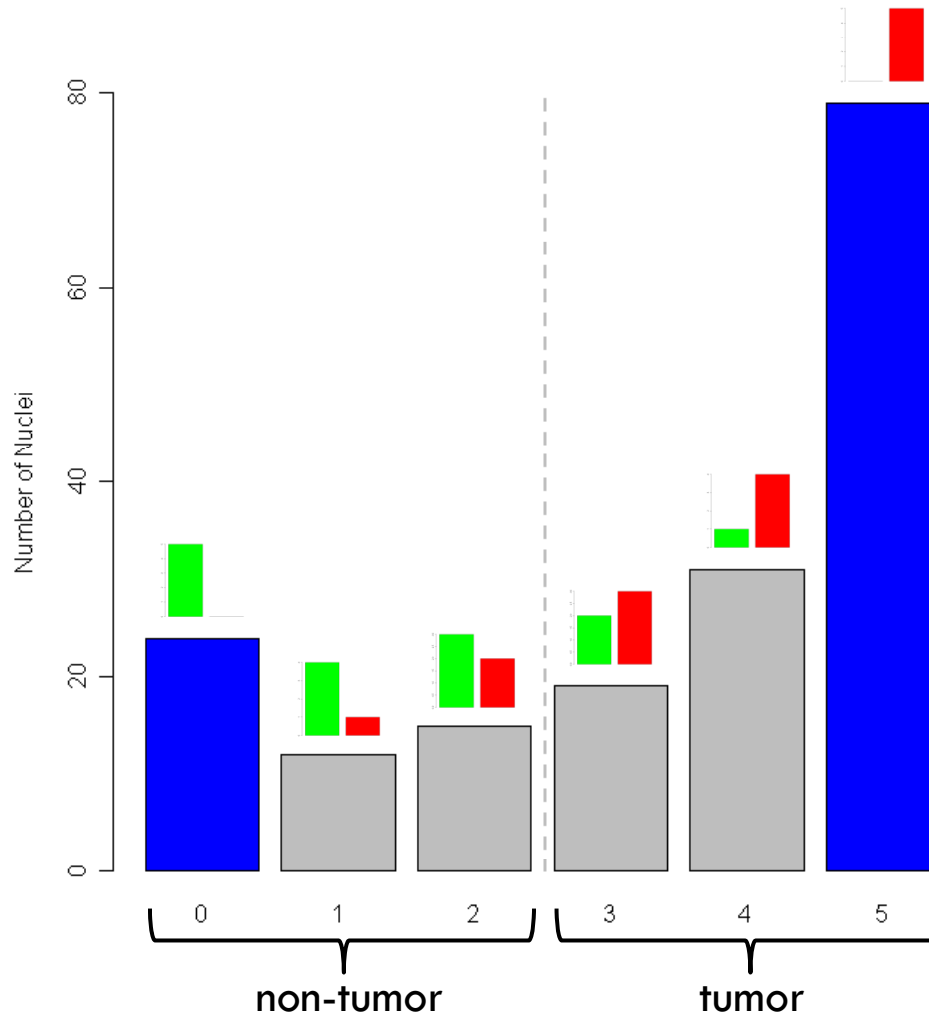
# TMA Classifier - Staining

The screenshot displays the TMA Classifier software interface. The main window shows a histological slide with a red box highlighting a specific cell. The interface is divided into three vertical panels, each showing a different view of the same cell. The left panel shows a low-magnification view, the middle panel shows a medium-magnification view, and the right panel shows a high-magnification view. A red crosshair is visible in the center of the highlighted cell in all three panels.

Below the slide, there is a control panel with six buttons arranged in two rows. The top row contains three buttons labeled +3, +2, and +1, all with a red background. The bottom row contains three buttons labeled -1, -2, and -3, all with a light gray background. The -2 button is highlighted with a blue border. In the center of the control panel, the text "3 / 222" is displayed.

+3	+2	+1	-1	-2	-3
Stained Certainly	Stained Probably	Stained Maybe	Clear Maybe	Clear Probably	Clear Certainly

# Inter Pathologists Consensus

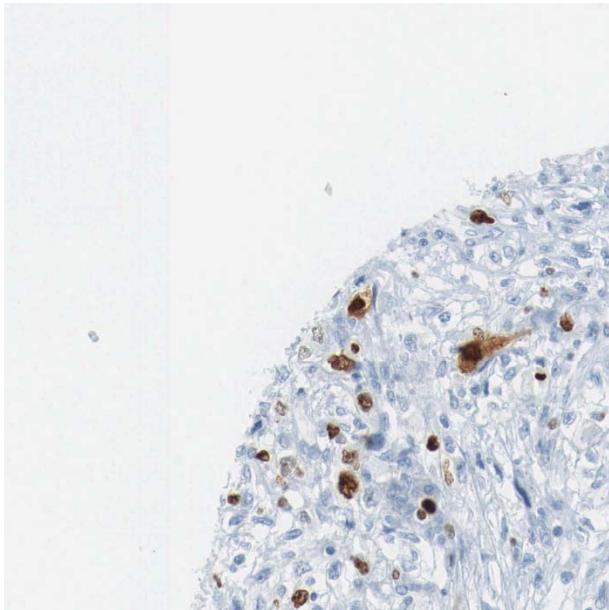


180 nuclei  
randomly  
drawn from  
9 spots.

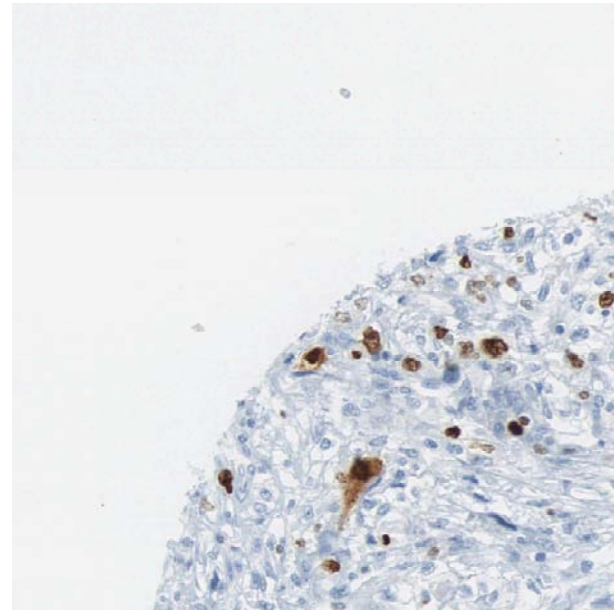
Agreement on  
105 nuclei.



# Intra Pathologist Evaluation



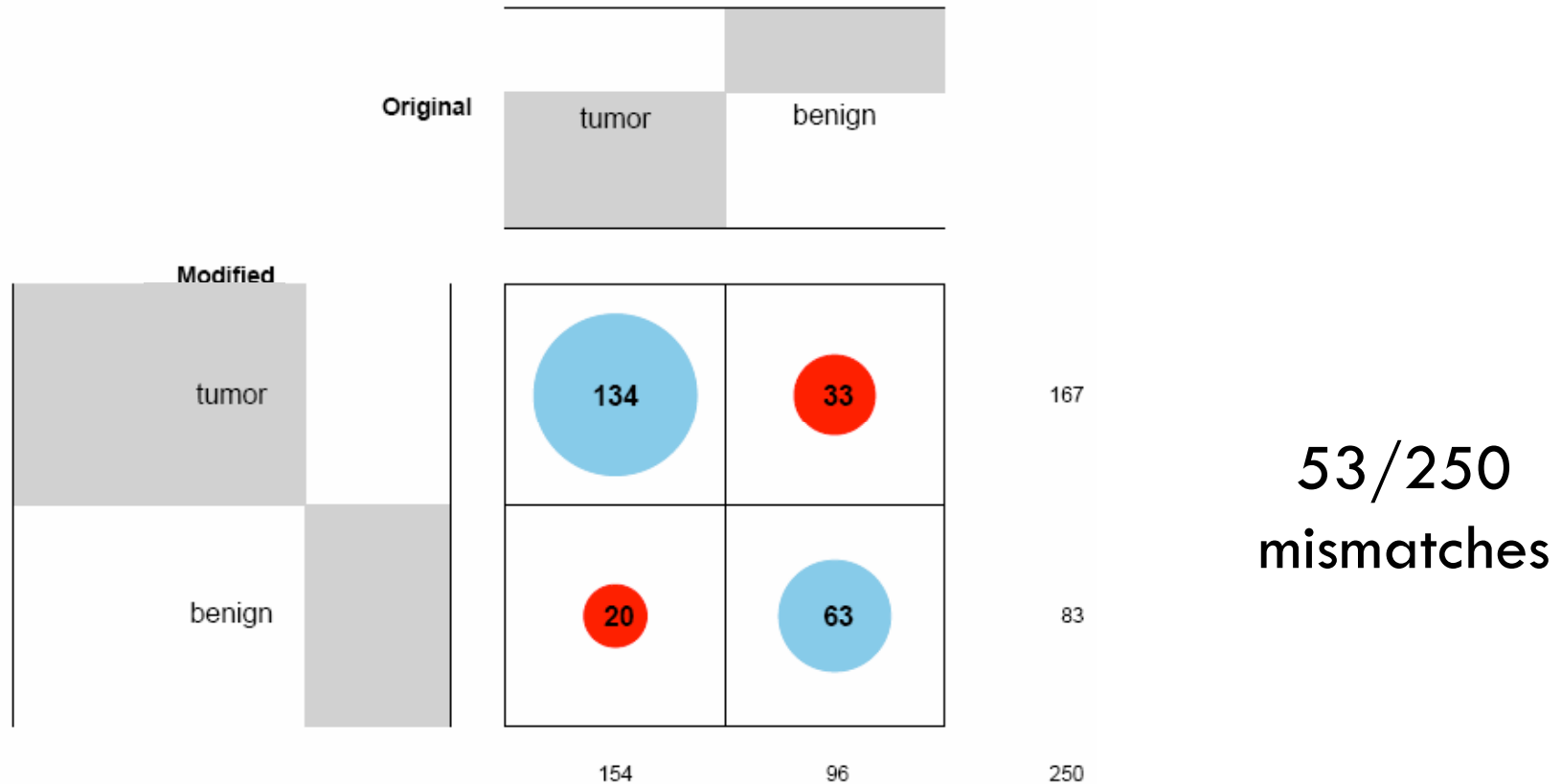
Original



Flipped & Rotated

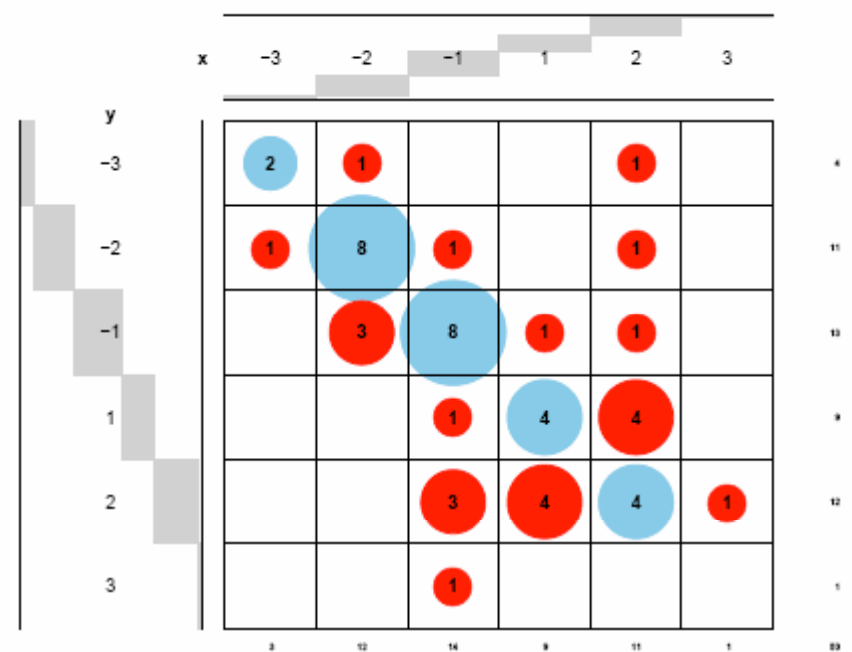
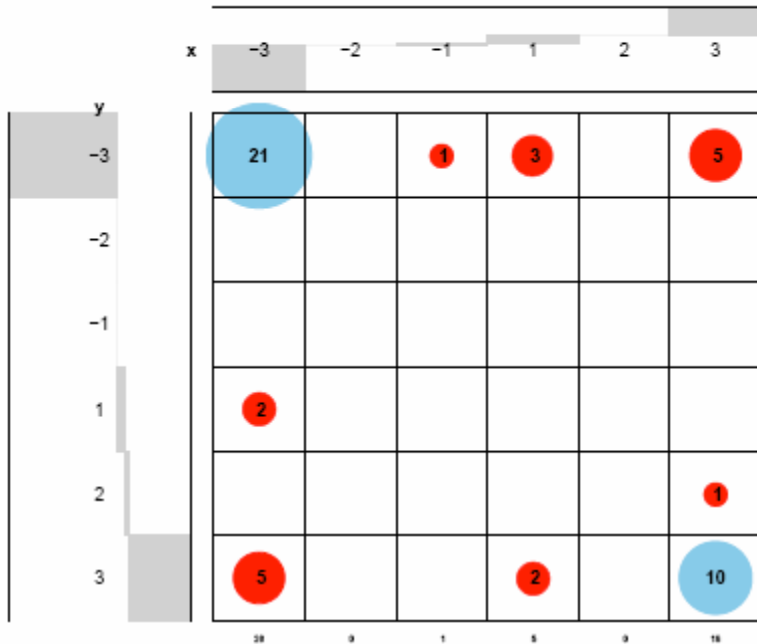
50 nuclei were repeated flipped and rotated to test the intra pathologist variability.

# Intra Pathologist Confusion Matrix

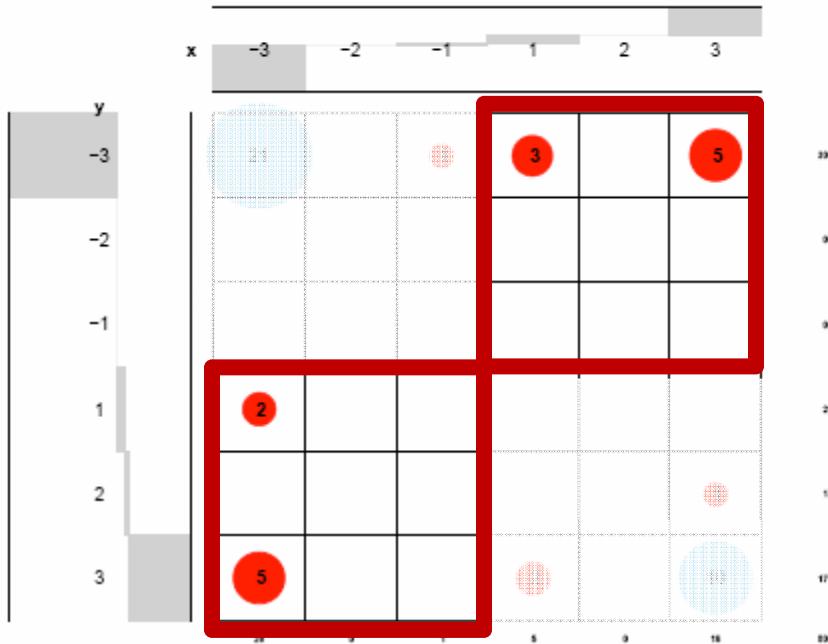


Baseline: Intra-Pathologists classification uncertainty of  $\sim 20\%$

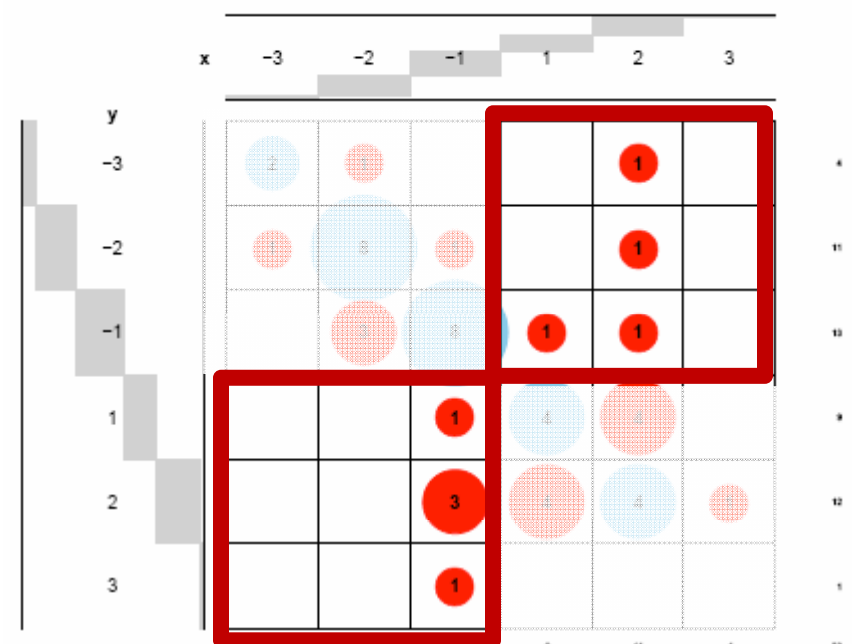
# Two Types of Pathologists



# Two Types of Pathologists



15 mismatches



9 mismatches

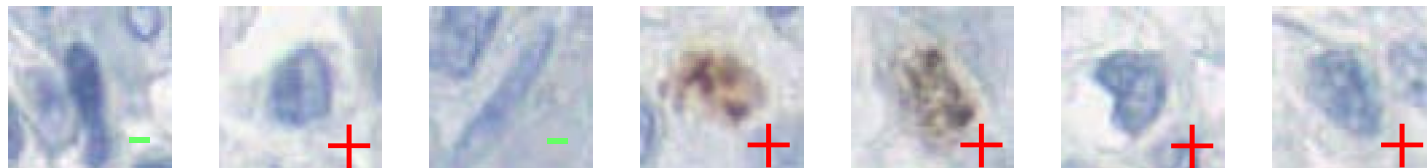


# Intra-Pathologist Agreement

5/5 pathologists agreed on +3



4/5 pathologists agreed on  $\pm 3$



# Intra-Pathologist Mismatches

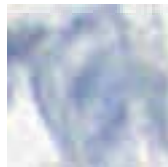
283  
4



302  
3



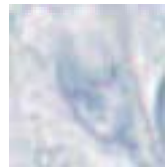
739  
3



1104  
3



1454  
3



1501  
3



1689  
3



138  
2



209  
2



386  
2



605  
2



1635  
2



1936  
2



2052  
2



2125  
2

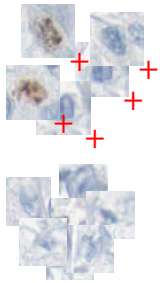


2337  
2

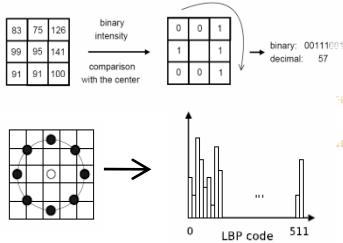


# Comp. Path. Framework

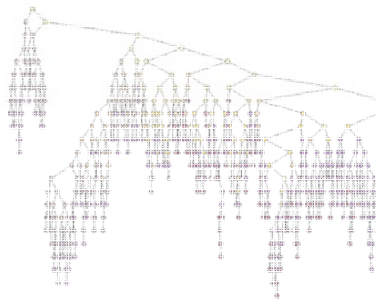
## 1 Training Samples



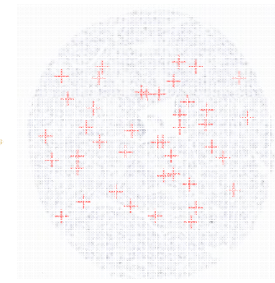
## 2 Feature Extraction



## 3 Random Forest Learning



## 4 Nuclei Detection

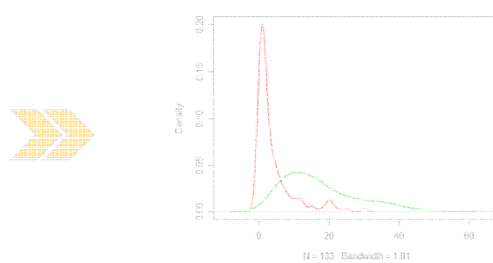


## 5 Staining Estimation

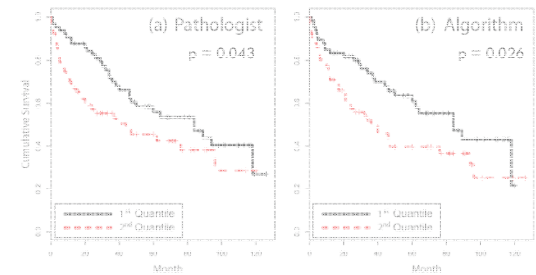
5%



## 6 Application to Patient Cohort



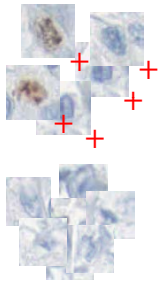
## 7 Estimated Marker Distribution



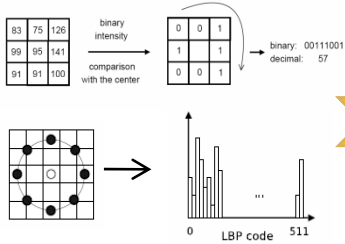
## 8 Survival Analysis

# Comp. Path. Framework

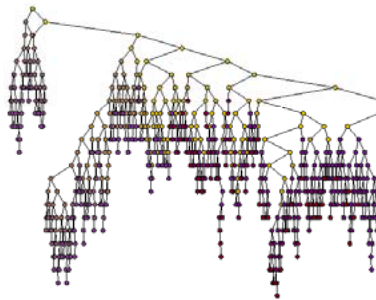
## 1 Training Samples



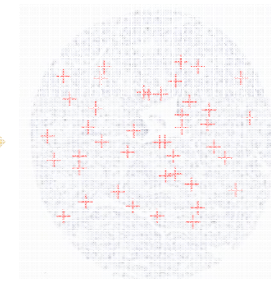
## 2 Feature Extraction



## 3 Random Forest Learning

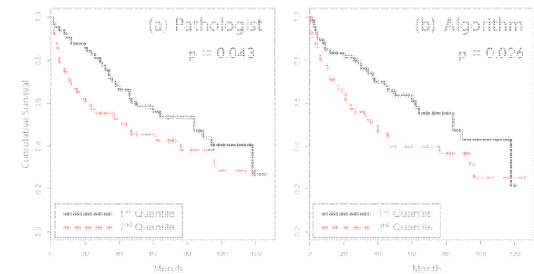
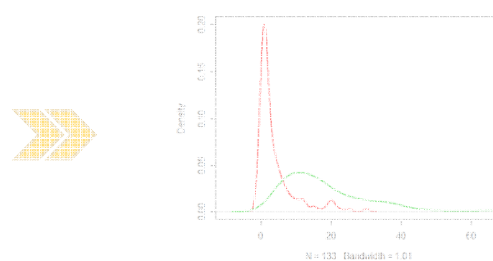


## 4 Nuclei Detection



## 5 Staining Estimation

5%



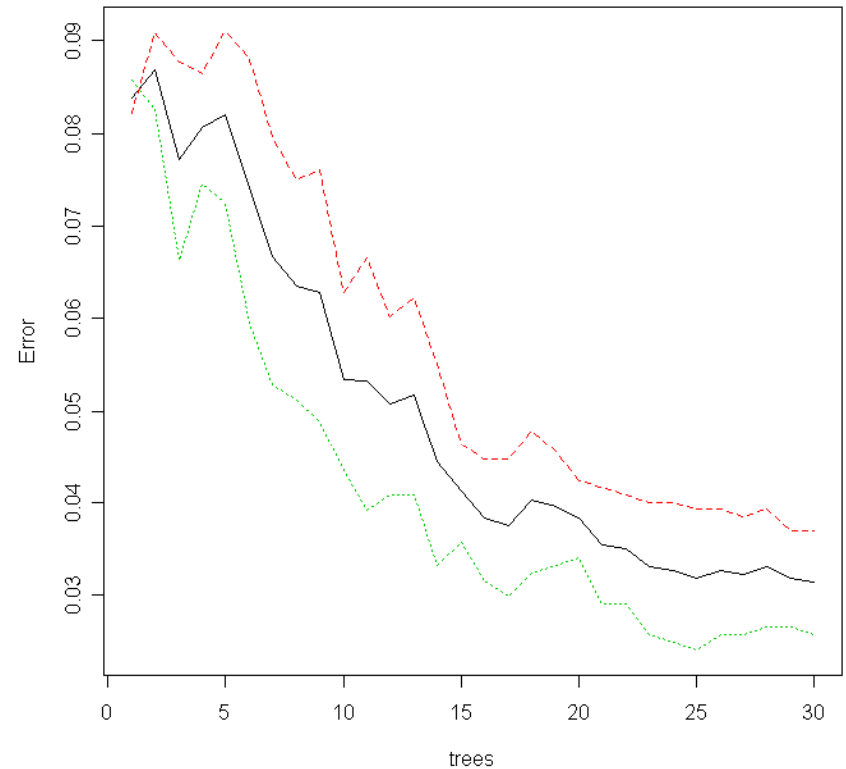
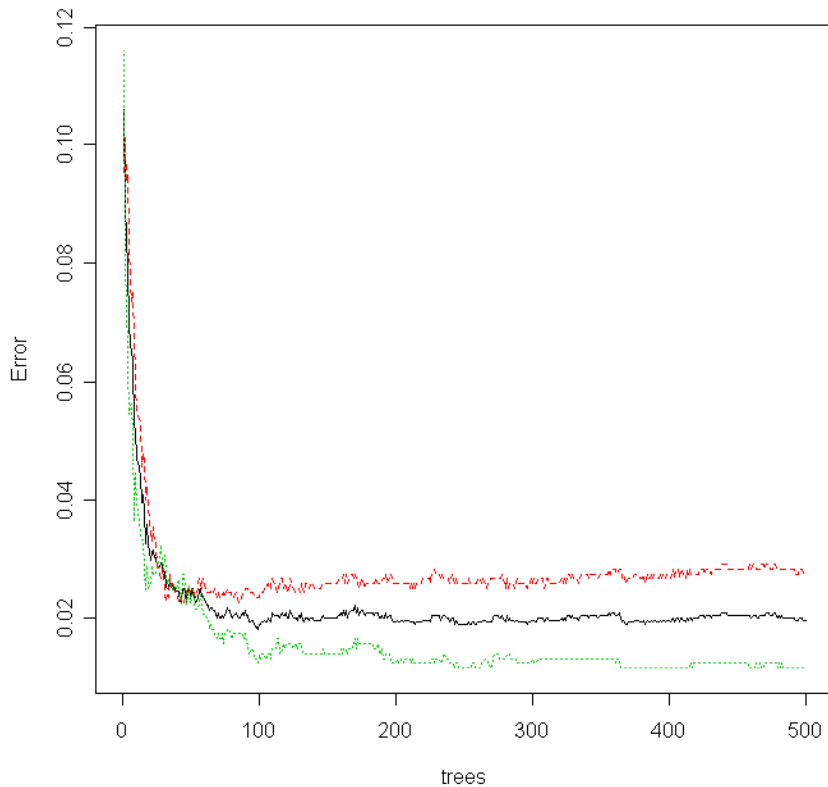
## 6 Application to Patient Cohort

## 7 Estimated Marker Distribution

## 8 Survival Analysis

# Cell Nuclei Detection

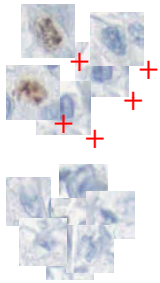
Random Forest with 20 features per split.  
Fast convergence.



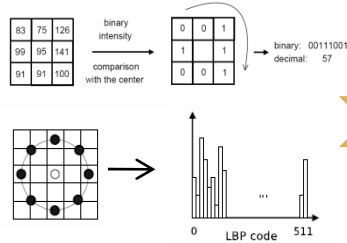


# Comp. Path. Framework

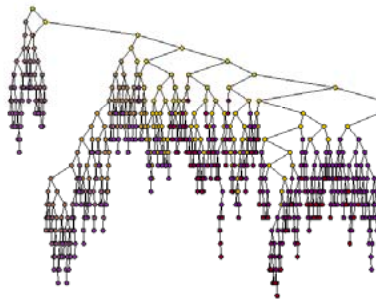
## 1 Training Samples



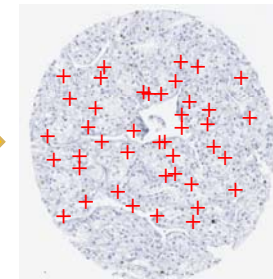
## 2 Feature Extraction



## 3 Random Forest Learning



## 4 Nuclei Detection

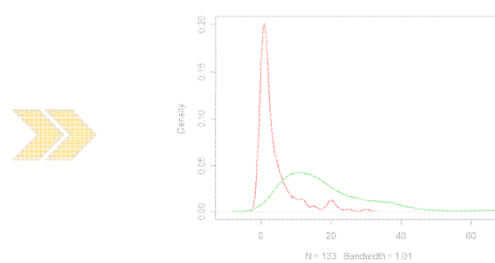


## 5 Staining Estimation

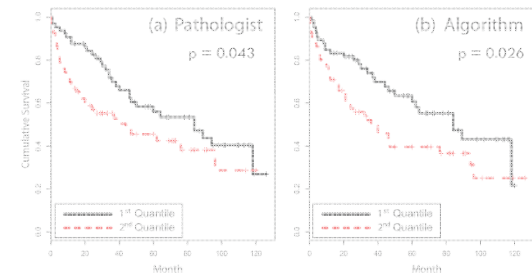
5%



## 6 Application to Patient Cohort

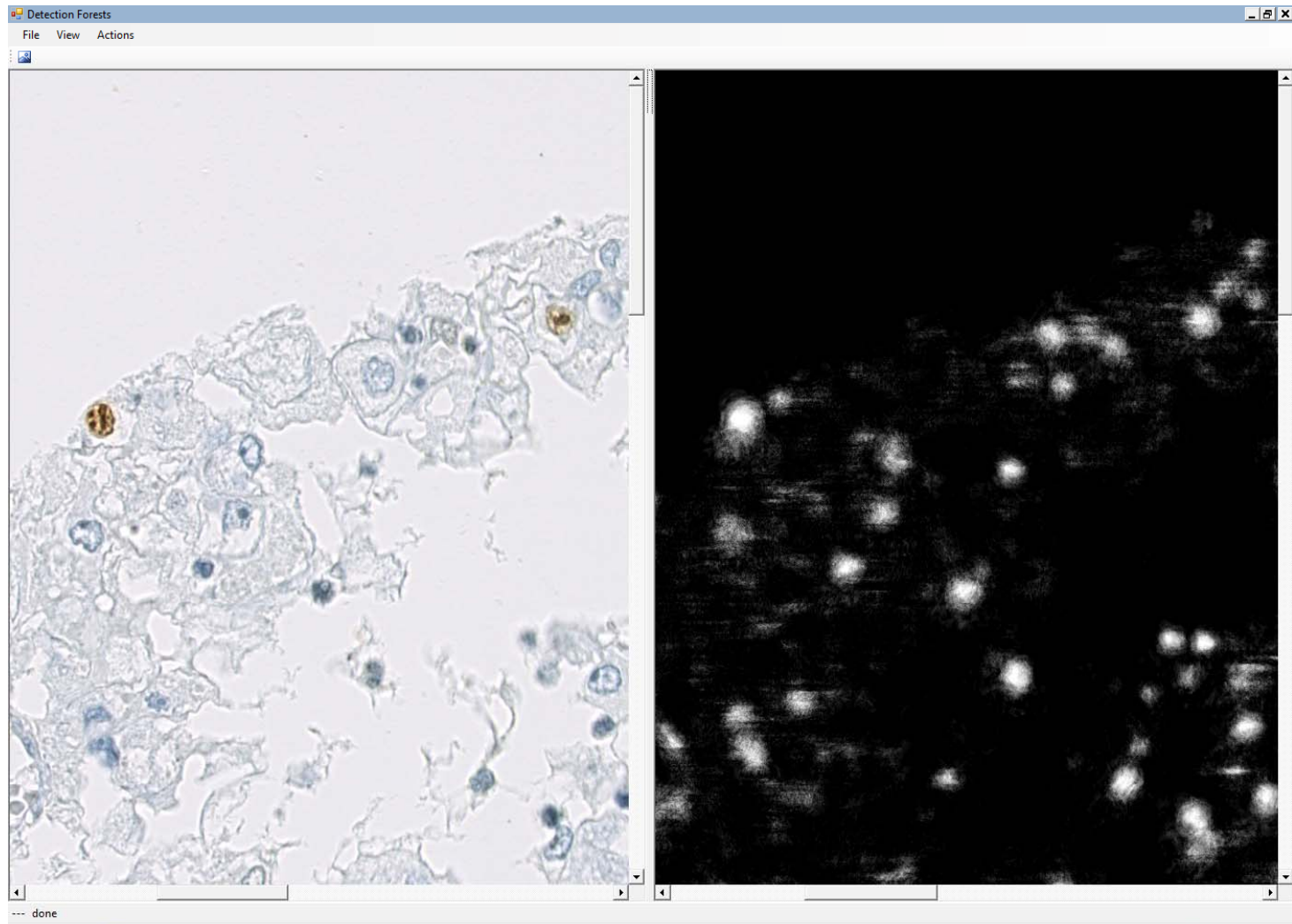


## 7 Estimated Marker Distribution

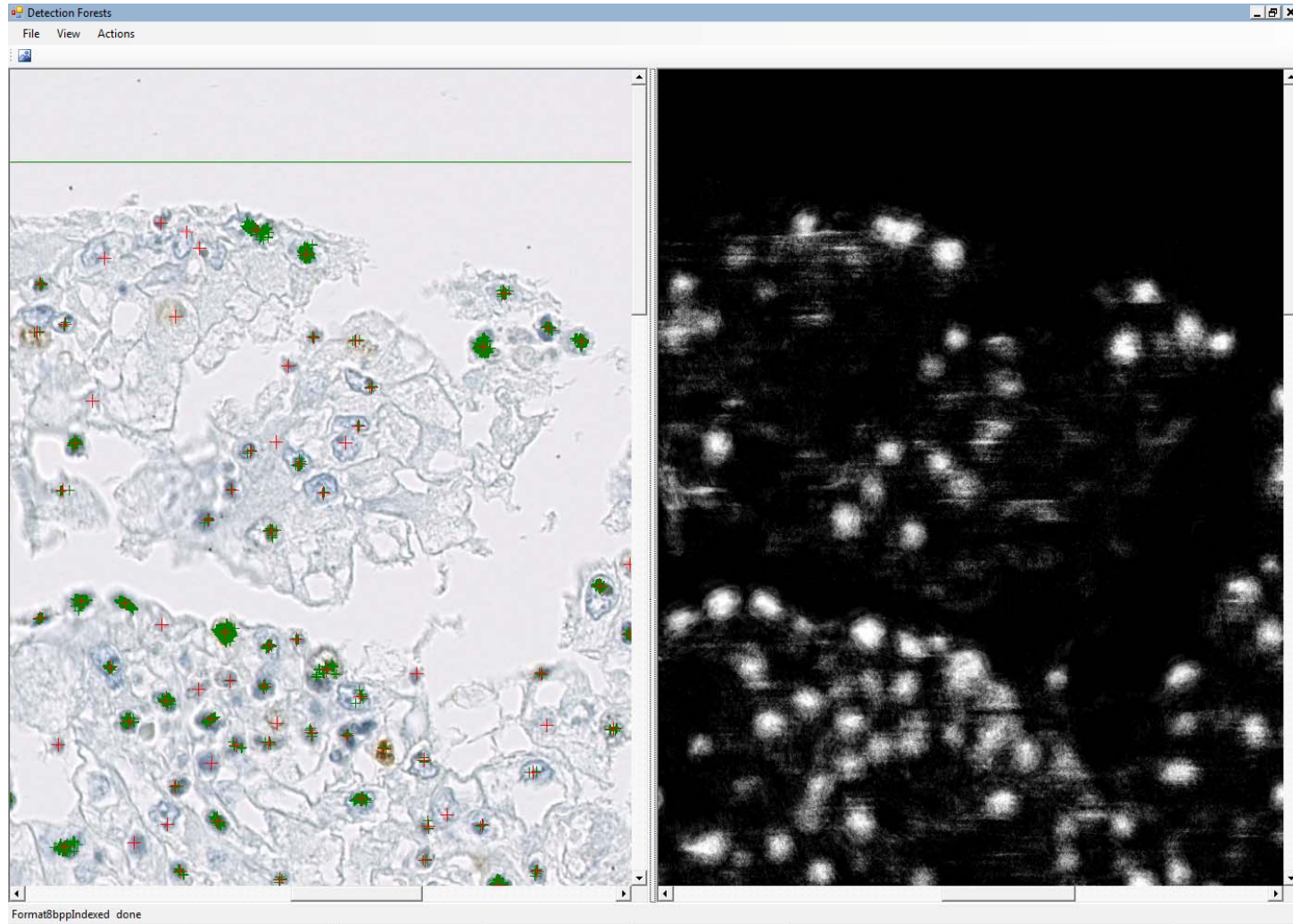


## 8 Survival Analysis

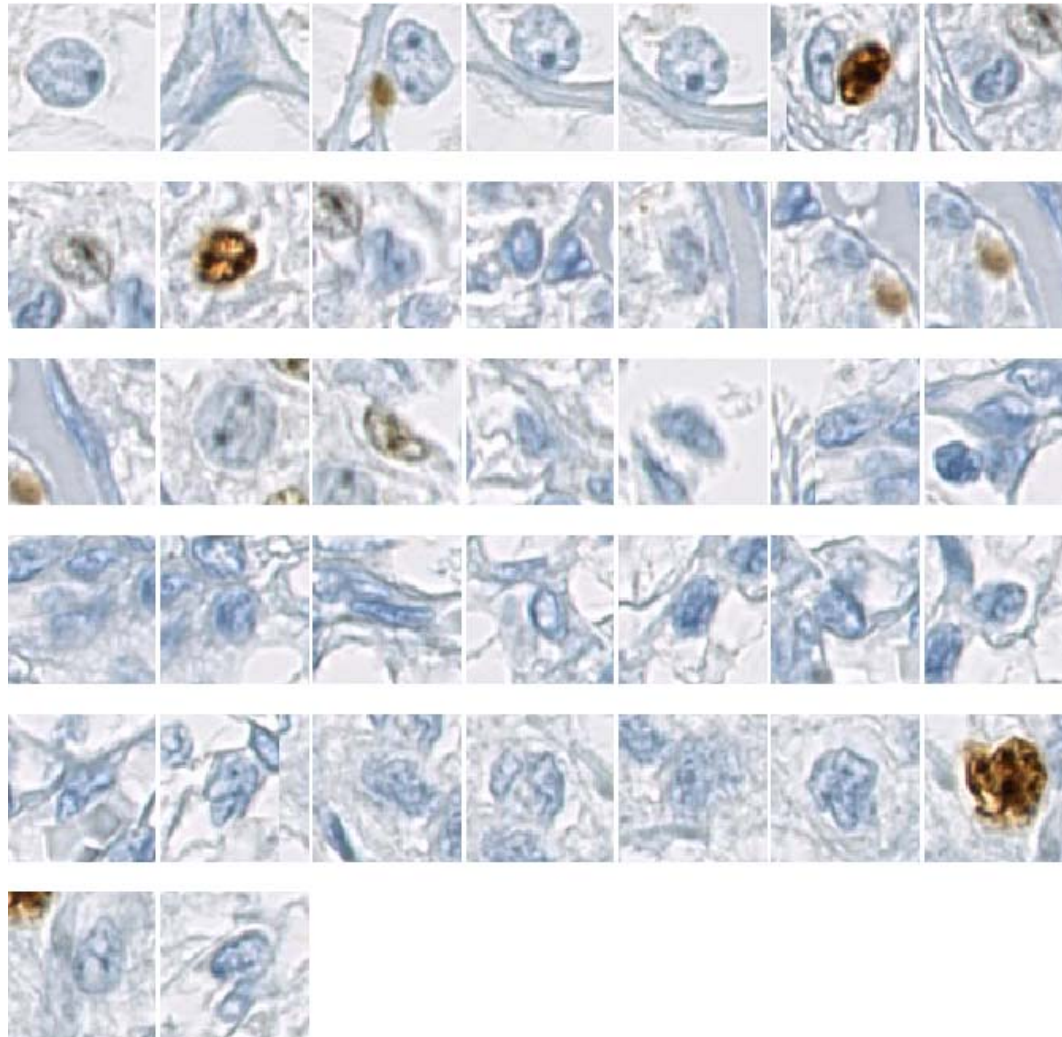
# Non Maxima Suppression



# Mean Shift with Circular Kernel



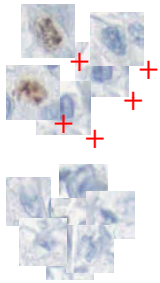
# Cell Nuclei Detection



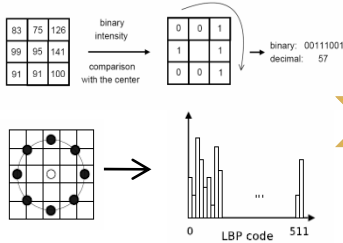


# Comp. Path. Framework

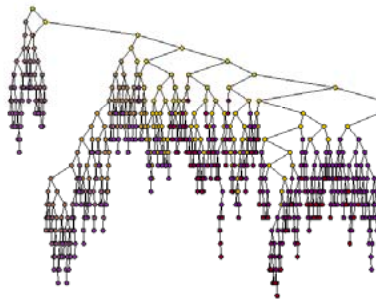
## 1 Training Samples



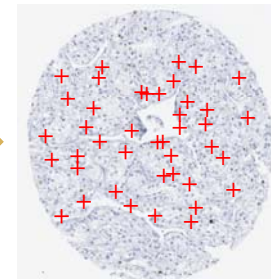
## 2 Feature Extraction



## 3 Random Forest Learning



## 4 Nuclei Detection

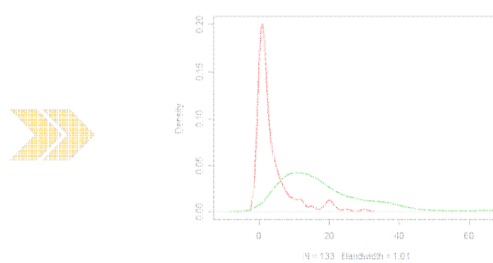


## 5 Staining Estimation

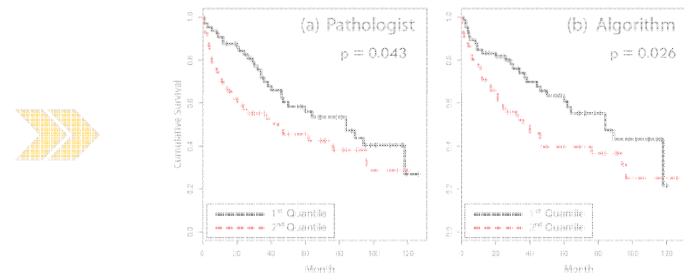
5%



## 6 Application to Patient Cohort



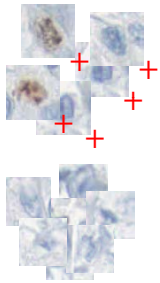
## 7 Estimated Marker Distribution



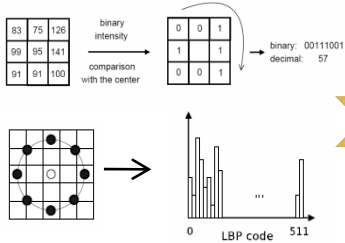
## 8 Survival Analysis

# Comp. Path. Framework

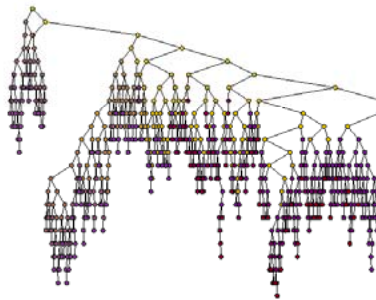
## 1 Training Samples



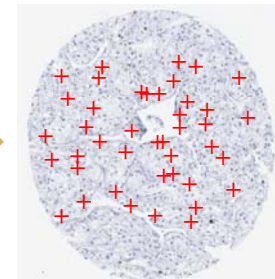
## 2 Feature Extraction



## 3 Random Forest Learning

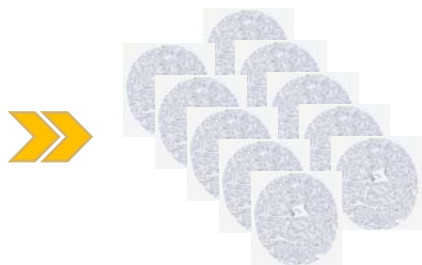


## 4 Nuclei Detection

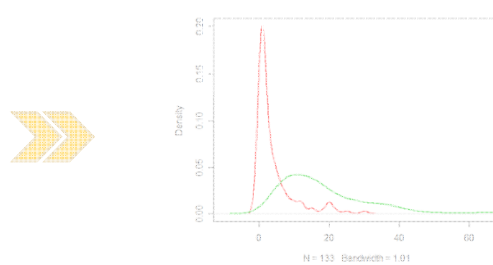


## 5 Staining Estimation

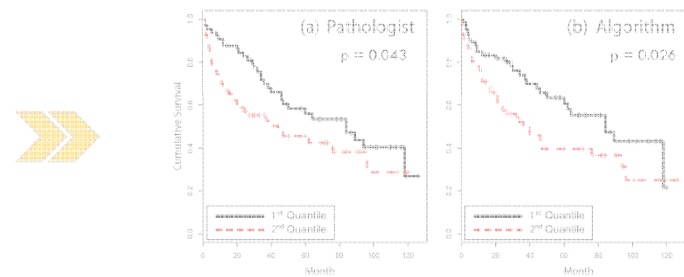
5%



## 6 Application to Patient Cohort



## 7 Estimated Marker Distribution

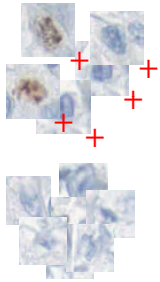


## 8 Survival Analysis

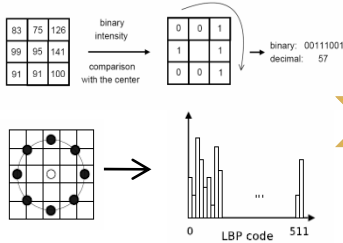


# Comp. Path. Framework

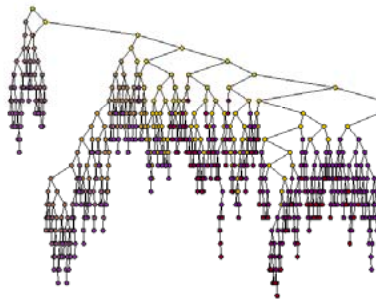
## 1 Training Samples



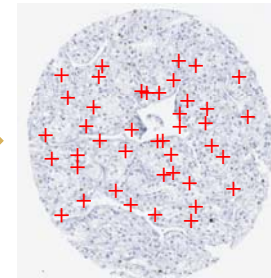
## 2 Feature Extraction



## 3 Random Forest Learning

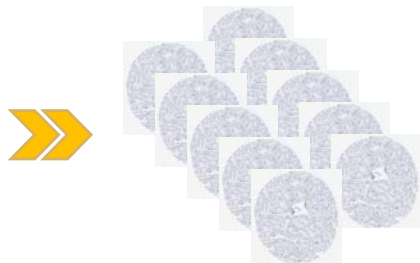


## 4 Nuclei Detection

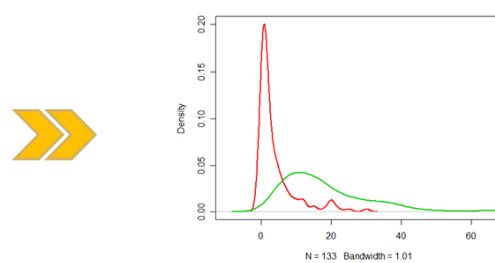


## 5 Staining Estimation

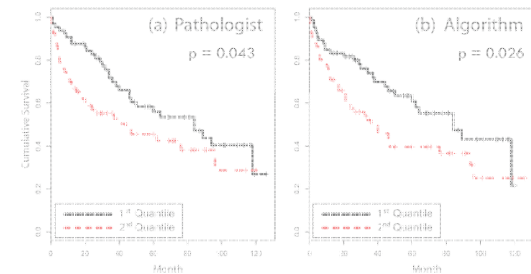
5%



## 6 Application to Patient Cohort

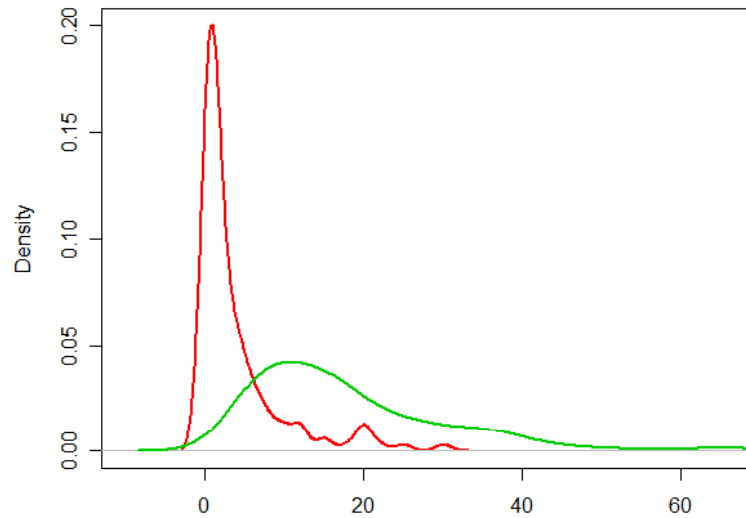
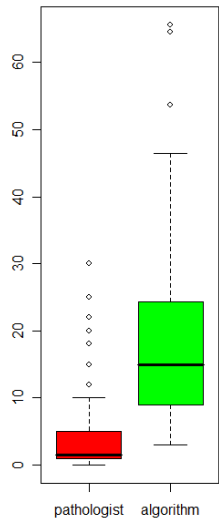


## 7 Estimated Marker Distribution

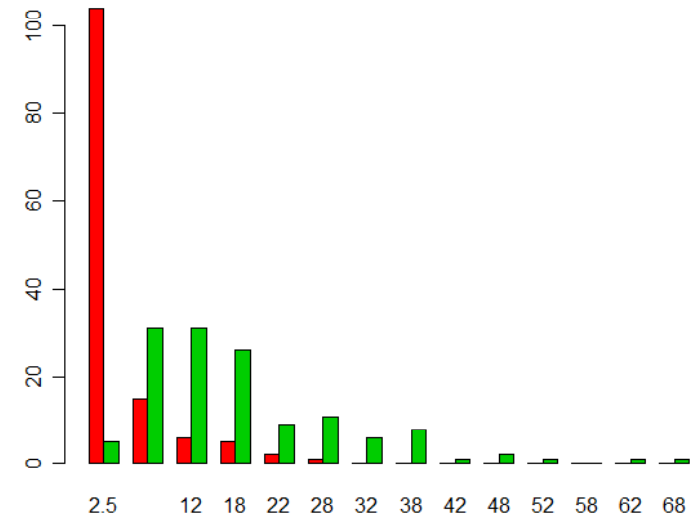


## 8 Survival Analysis

# Estimation Distributions

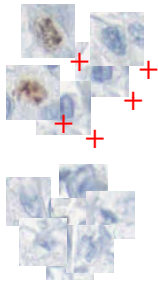


N = 133 Bandwidth = 1.01

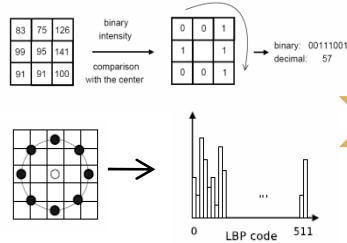


# Comp. Path. Framework

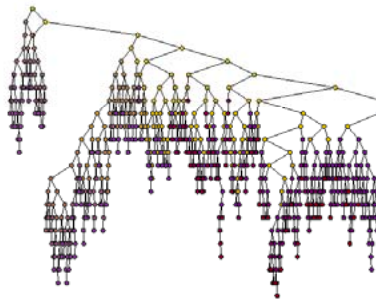
## 1 Training Samples



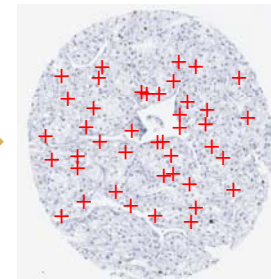
## 2 Feature Extraction



## 3 Random Forest Learning

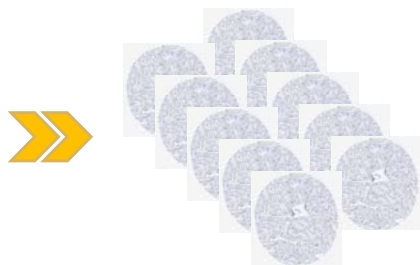


## 4 Nuclei Detection

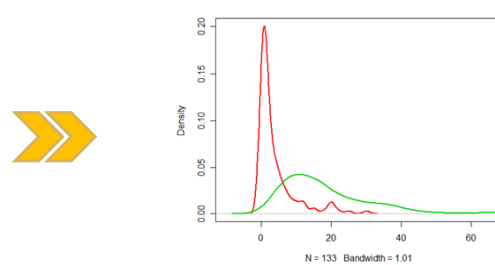


## 5 Staining Estimation

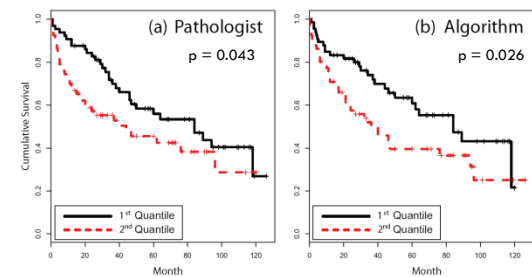
5%



## 6 Application to Patient Cohort

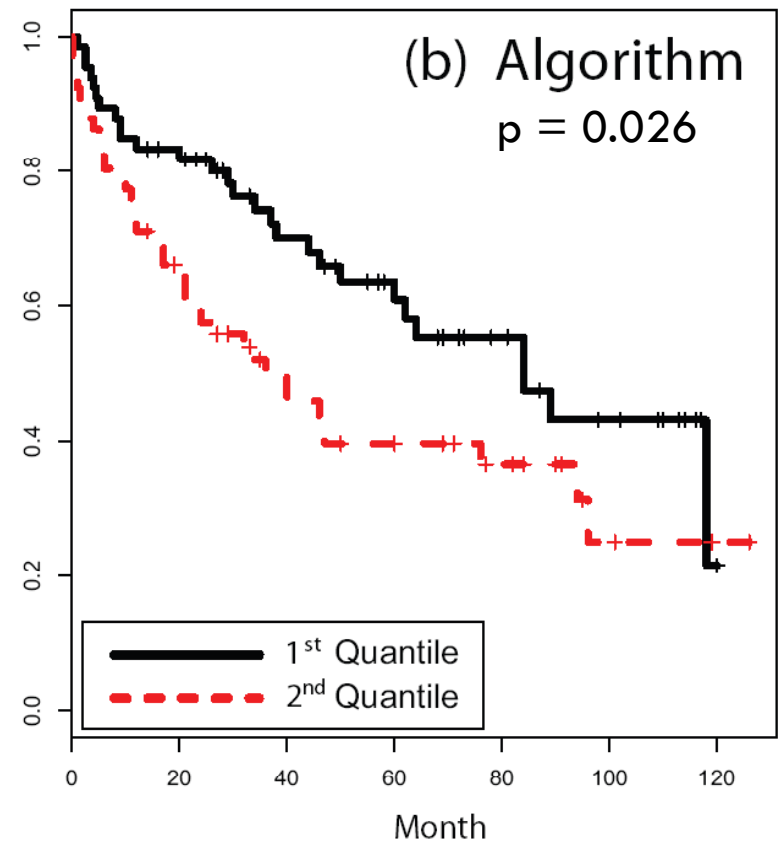
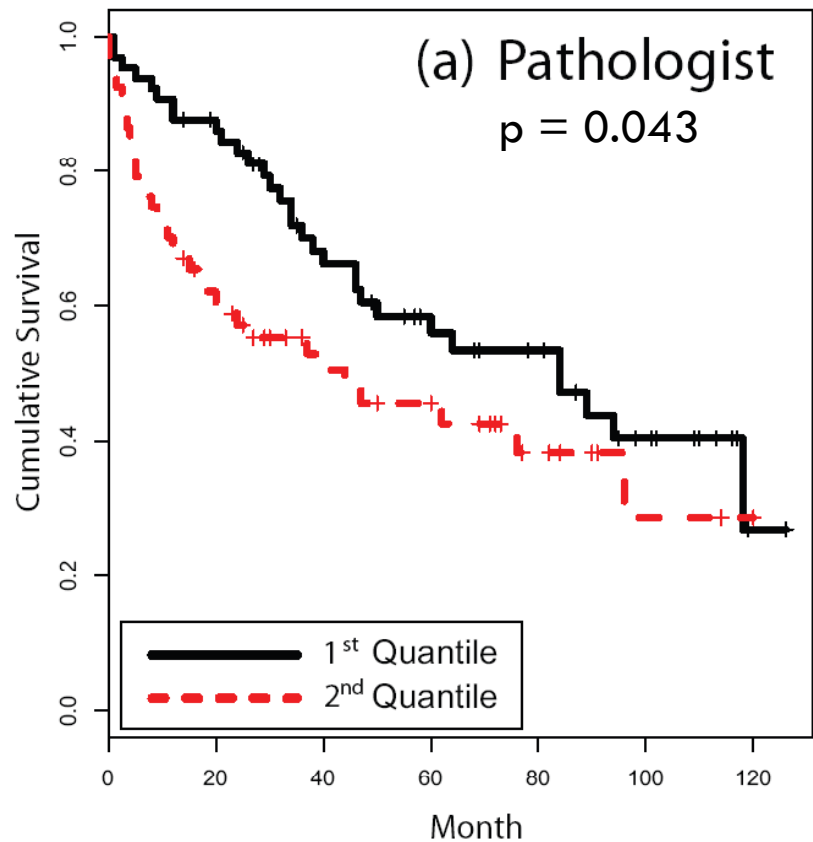


## 7 Estimated Marker Distribution

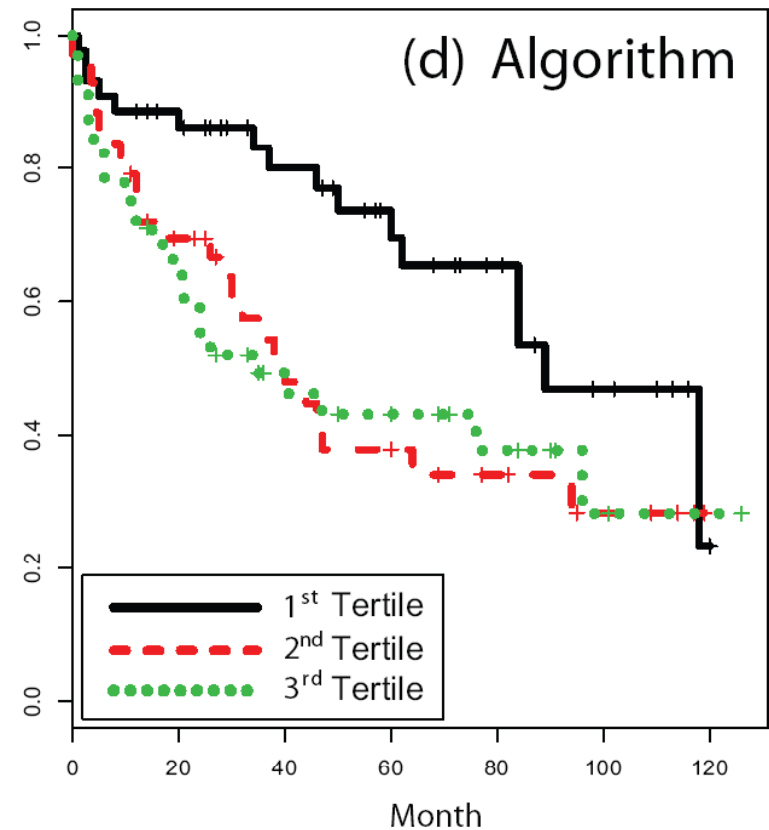
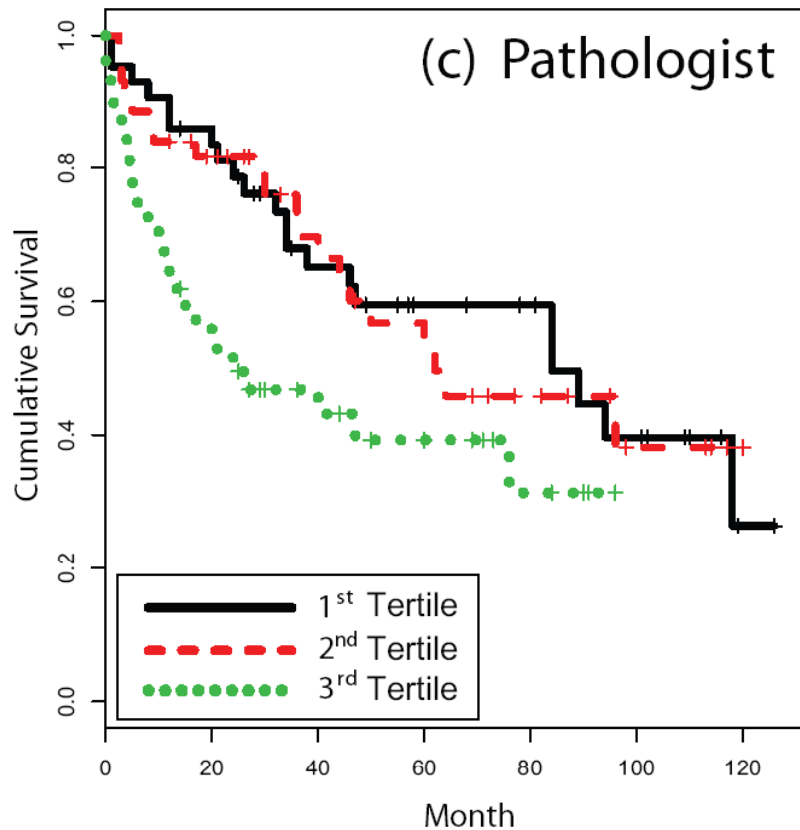


## 8 Survival Analysis

# Survival Analysis



# Survival Analysis



# Acknowledgements



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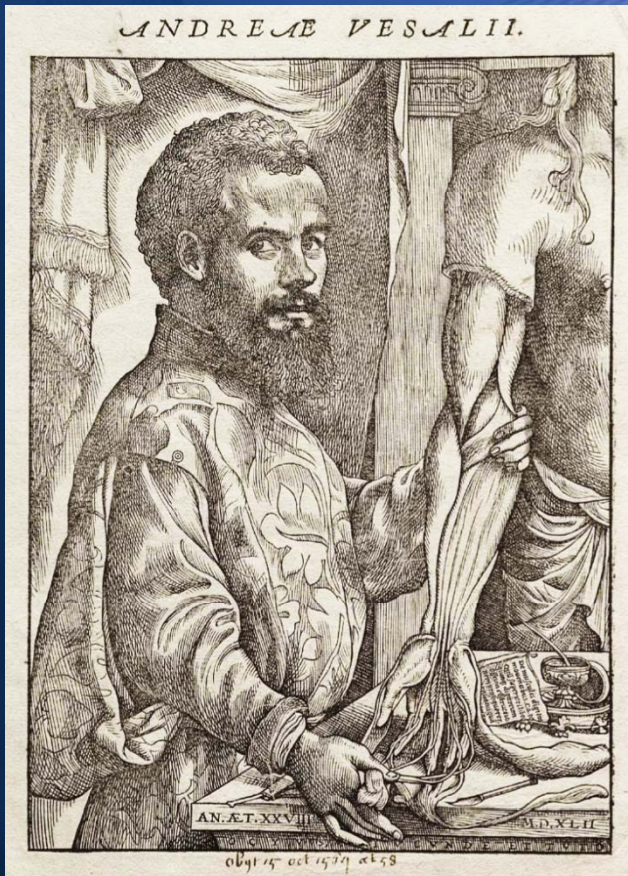
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Thank you for your attention!

Questions?